IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION and ASTEX THERAPEUTICS LTD. Plaintiffs, v. MSN PHARMACEUTICALS INC. and MSN LABORATORIES PVT. LTD., Defendants.	C.A. No. 21-870-GBW (CONSOLIDATED)

MSN'S OPENING POST-TRIAL BRIEF

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I. INTRODUCTION

Novartis wrongfully attempts to foreclose generic competition for its CDK4 inhibitor, ribociclib, with the three asserted patents, all of which are invalid. Novartis' first patent to a CDK4 inhibitor, the '225 patent, is invalid for lack of written description and non-enablement, because Novartis claimed more than it had a right to claim. The '225 patent fails to inform a POSA that the inventors had possession of the alleged invention, and the specification does not enable a POSA to make and use the full scope of claim 1. Novartis later obtained the '630 and '355 patents, which improperly extend its monopoly on ribociclib for almost three more years. The '630 and '355 patents are invalid as obvious over admitted prior art Compound 338 in combination with the Pfizer SAR Papers. The sole difference between Compound 338 and ribociclib is a single nitrogen atom—which Novartis' scientists termed the "magic N"—that the Pfizer SAR Papers had praised as turning potent (but non-selective) CDK4 inhibitors into highly selective CDK4 inhibitors. A POSA would have chosen the potent, but non-selective, CDK4 inhibitor Compound 338 as a lead compound based on its structural similarity to the known CDK4 inhibitor palbociclib. And in view of the Pfizer SAR Papers, it would have been exceedingly obvious to add the "magic N" to Compound 338 to increase its selectivity, thus achieving ribociclib with more than a reasonable expectation of success. The '630 and '355 patents are also invalid for obviousness-type double patenting over claim 7 of the '225 patent, which claims Compound 338, in combination with the Pfizer SAR Papers.

Because the patents-in-suit are invalid, the Court should thus issue judgment in MSN's favor.

A. CDK4 was known as a therapeutic target through the teachings of the Pfizer SAR Papers.

Cyclin-dependent kinases, or CDKs, are effectively "switches" that control transitions

from one phase of the cell cycle to another, which is important for cell division. Defendants' Findings of Fact ("FOF") at ¶ 1. CDK4 was highlighted as a potential drug target: by 2004, it was known that compounds that specifically inhibited CDK4 exhibited efficacy in *in vivo* tumor models. *Id.* at ¶ 2. One such compound, PD 0332991, known as palbociclib, had been identified as a potent inhibitor of CDK4/6 that exhibited antitumor activity. *Id.* at ¶ 3.

A POSA also understood the active regions of the CDK4 binding site and how to design compounds, or ligands, that target them. In particular, a POSA understood that they should be targeting the ATP binding site of CDK4. *Id.* at ¶ 4. Although there was limited structural information on the CDK4 ATP binding site, there was substantial structural information regarding a related CDK enzyme, CDK2, that POSAs used in designing CDK4 ligands. *Id.* at ¶ 5. A POSA also knew that the CDK4 ATP binding site could be divided into four subregions: (1) the hinge region, (2) the specificity surface, (3) the ribose/phosphate site, and (4) the Phe80 pocket. FOF at ¶ 6.

Unrebutted testimony showed that, based on the Pfizer SAR Papers—Barvian 2000, Toogood 2001, VanderWel, and Toogood 2005—a POSA developed an understanding of the structure-activity relationship (SAR) of CDK4-inhibiting ligands, such as palbociclib and similar compounds, which engage these four subregions of the CDK4 ATP binding site.

First, Barvian 2000 and Toogood 2001 together would have taught a POSA that an aminopyrimidine group was critical for forming two hydrogen bonds to the hinge region of CDK4, which orients the ligand within the ATP binding site. *Id.* at ¶ 7.

Second, Barvian 2000 and VanderWel would have taught a POSA that placing an aromatic group that was *para*-substituted with a basic heterocycle, particularly piperazine, off of the aminopyrimidine amine to interact with the specificity surface profoundly increases potency for

CDK4. *Id.* at ¶ 8. Toogood 2005 further would have taught a POSA that substituting a 2-pyridyl group for a phenyl group off of the aminopyrimidine amine profoundly improves selectivity for CDK4 over other CDKs. *Id.*

Third, Barvian 2000 and Toogood 2005 would have taught a POSA that the ribose/phosphate site could accommodate a wide variety of large, cyclic, hydrophobic moieties, and that placing a cyclopentyl group in the ribose/phosphate site offers the best balance of selectivity and potency for CDK4. *Id.* at ¶ 9.

Fourth, VanderWel and Toogood 2005 would have taught a POSA that small electron-withdrawing groups that interact with the Phe80 pocket improve potency for CDK4. *Id.* at ¶ 10. Toogood 2005 further would have taught a POSA that an out-of-plane carbonyl-containing group at this position forms a favorable interaction with CDK4. *Id*.

A POSA reading the Pfizer SAR Papers would have recognized that palbociclib is a potent and selective CDK4 inhibitor because it optimally interacts with the four subregions within the ATP binding site: it contains an aminopyrimidine moiety to engage the hinge region to dock the molecule into the ATP binding site, and provides clear trajectories for other portions of the molecule toward the other subregions of the binding site; a pyridyl-piperazine group to engage the specificity surface: a cyclopentyl group to occupy the ribose/phosphate site; and a small, out-of-plane carbonyl-containing group projected towards the Phe80 pocket. *Id.* at ¶ 11.

B. Novartis' CDK4 project piggy-backed off of Pfizer's work to achieve a rapid "me too" "fast follower" compound, ribociclib.

In July 2005, Christopher Brain started a new project at Novartis: to discover a new CDK4 inhibitor. FOF at ¶ 12. His first activities included reading the published literature on Pfizer's potent and selective "gold standard" CDK4 inhibitor, palbociclib, and presenting a summary of the SAR disclosed in the Pfizer SAR Papers to the CDK4 team. *Id*. Based on their "close" structural

similarity to palbociclib, but outside the scope of Pfizer's patents, Dr. Brain selected several existing pyrrolopyrimidine compounds from Novartis' JAK3 program that he wanted to transform into selective CDK4 inhibitors, using the Pfizer SAR Papers as a guide. *Id*. Novartis intended to use this less scientifically challenging approach to rapidly develop their own, "me too," "fast follower" compound to compete with Pfizer. *Id.* at ¶ 13.

On May 26, 2006, Novartis filed a provisional patent application that matured into the '225 patent and was published as the Brain PCT. *Id*. The '225 patent and Brain PCT do not specifically disclose ribociclib, because, as Plaintiffs admit, ribociclib was not invented yet. *Id.* at ¶ 14.

Meanwhile, Novartis continued to modify its pyrrolopyrimidine compounds in order to investigate how information from the Pfizer SAR Papers could be used to drive selectivity towards CDK4. *Id.* at ¶ 15. One teaching from the Pfizer SAR Papers that was of particular interest to Novartis was the inclusion of a nitrogen-containing pyridyl group on the C2 side chain of palbociclib in place of a carbon-containing phenyl group, a modification that the Novartis scientists referred to as the "magic N" for its ability to drive selectivity towards CDK4. *Id.* at ¶ 16. Novartis hoped to apply the selectivity obtained with the "magic N" to its compounds. *Id.* at ¶ 17. And indeed, during its research, Novartis found that the same modification on its pyrrolopyrimidine compounds—replacing the carbon-containing phenyl group at the C2 position with the "magic N"-containing pyridyl group—produced the same result. *Id.*

Compound 338 was conceived by Bharat Lagu, either alone or in collaboration with Yaping Wang, on January 16, 2007, and reduced to practice by Dr. Wang on January 25, 2007. *Id.* at ¶ 18. By March 2007, Compound 338 had become a compound of particular interest, and one of Novartis' "most attractive compounds at present in terms of selectivity and cellular activity." JTX0043-0001; Tr. 297:4-298:17 (Brain). However, Novartis still sought to modify Compound

338. JTX0043-0005; Tr. 298:18-25 (Brain).

On April 3, 2007, Dr. Brain conceived ribociclib—in which he replaced the carbon-containing phenyl group at the C2 position of Compound 338 with the "magic N"-containing pyridyl group—"[t]o improve the selectivity of [Compound 338]", which omits the pyridyl nitrogen; it was reduced to practice the same day. FOF at ¶ 19. Dr. Brain had noted from the Pfizer SAR Papers that the same modification in Pfizer's palbociclib compound resulted in a slight loss of potency for CDK4, but significantly increased selectivity. *Id.* at ¶ 20. Likewise, Dr. Brain predicted that, "[b]ased on existing SAR," inserting the "magic N" into Compound 338 would somewhat reduce potency for CDK4 but significantly increase selectivity, which is exactly what happened. *Id.*

On August 22, 2008, Novartis filed a new provisional patent application that matured into the '630 and '355 patents. *Id.* at ¶ 21. Each patent states: "the following compounds (from [Brain PCT]) of table 3 represents the closest prior art to the chemotype of the presently claimed invention." *Id.* at ¶ 22. Compound 338 (listed as compound 200) is one of the three compounds identified. *Id.* Each patent also states: "The following table 4 shows the inhibition against relevant targets of compounds of the prior art as compared to compounds of the present invention:"

TABLE 4

Compound Number	IC50 (μM)	Selectivity
200 (prior art)	CDK4: 0.005 CDK1: >1.6 CDK2: >1.4	
201(prior art)	CDK4: 0.11 CDK1: 7.5 CDK2: 10.3	
202 (prior art)	CDK4: 2.5 CDK1: >15 CDK2: >15	
74 of present application	CDK4: 0.01 CDK1: 113 CDK2: 76	Greater than 11,000 fold selective against CDK4
63 of present application	CDK4: 0.008 CDK1: >15 CDK2: >15	
26 of present application	CDK4: 0.026 CDK1: >15 CDK2: >15	

Id. The patents also present the "results of cell cycle analysis performed with the presently claimed

compounds and compound 200 [(Compound 338)] of the prior art." *Id*.

II. MSN HAS PROVEN THAT CLAIM 1 OF THE '355 PATENT AND CLAIM 6 OF THE '630 PATENT ARE OBVIOUS OVER COMPOUND 338 IN VIEW OF THE PFIZER SAR PAPERS

The asserted claims of the '355 and '630 patents are directed to the compound ribociclib and its use to treat carcinoma of the breast. JTX0002-0072 (claim 1); JTX0004-0073 (claim 6). The asserted claims would have been obvious to a POSA over Compound 338 in view of the Pfizer SAR Papers. A POSA would have selected Compound 338 as a lead compound and made obvious modifications to arrive at claim 1 of the '355 patent and claim 6 of the '630 patent.

A. Compound 338 and "statements explanatory thereof" is admitted prior art with respect to the '355 and '630 patents.

Because the specification of the '355 and '630 patents identifies Compound 338 as "prior art" and it represents the work of someone other than the inventor of ribociclib, Compound 338 is prior art. In addition, because the specification makes those admissions in the context of distinguishing ribociclib's "surprising and unexpected" selectivity based on Compound 338's potency and selectivity, the data also forms part of the prior art.

1. Compound 338 is admitted prior art and the work of another.

The '355 and '630 patents state that three compounds[1] from Brain PCT, including Compound 338, represent "the closest prior art to the chemotype of the presently claimed invention" and identify Compound 338 (listed as compound 200) as "prior art" multiple times in the specification and prosecution history. FOF at ¶ 24. "[A] statement by an applicant during prosecution identifying certain matter not the work of the inventor as 'prior art' is an admission that the matter is prior art." *Riverwood Int'l Corp. v. R.A. Jones & Co., Inc.*, 324 F.3d 1346, 1354

[1] However, during prosecution, the applicants asserted that one of these three compounds was not, in fact, prior art. *See* JTX0007-4315.

(Fed. Cir. 2003) (*citing In re Nomiya*, 509 F.2d 566, 571 n. 5 (C.C.P.A. 1975) ("[A] statement by an applicant, whether in the application or in other papers submitted during prosecution, that certain matter is 'prior art' to him, is an admission that that matter is prior art for all purposes, whether or not a basis in § 102 can be found for its use as prior art."). Further, unrebutted testimony showed that ribociclib was conceived by Dr. Brain and Compound 338 was conceived by Dr. Lagu (possibly in collaboration with Dr. Wang). Since Compound 338 is not the work of inventor Dr. Brain, the statements in the '355 and '630 patents and prosecution history that Compound 338 is prior art are admissions that the matter is prior art. *See Riverwood*, 324 F.3d at 1354; *see also Aktiebolaget Karlstads Mekaniska Werkstad v. U.S. Int'l Trade Comm'n*, 705 F.2d 1565, 1574 (Fed. Cir. 1983) (determining that portions of prior patent of one co-inventor was admitted prior art to joint inventive entity).

2. The scope of the admitted prior art.

"It is necessary to consider everything [patentee has] said about what is prior art to determine the exact scope of the[] admission." *Nomiya*, 509 F.2d at 571. Here, in addition to identifying Compound 338 and other compounds as "prior art," the '355 and '630 patents state that the compounds are "from" Brain PCT, identified by its application number, which "generically discloses compounds of this class." FOF at ¶ 26. The '355 and '630 patents also disclose data in Table 4 "show[ing] the inhibition against relevant targets of compounds of the prior art as compared to compounds of the present invention," and listing IC50 values for "prior art" Compound 338 of 5 nM for CDK4, >1.6 μM for CDK1, and >1.4 μM for CDK2. *Id.* at ¶ 27. Further, the '355 and '630 patents present cell cycle analysis results for "prior art" Compound 338. *Id*. In addition, Brain PCT lists IC50 values for Compound 338 of >1 μM for CDK4, <10 μM for CDK1, and <10 μM for CDK2. *Id.* at ¶ 28. All of this explanatory disclosure regarding Compound 338 is within the scope of the admitted prior art. *See Nomiya*, 509 F.2d at 571 ("By filing an

application containing Figs. 1 and 2, labeled prior art, *ipsissimis verbis*, ***and statements explanatory thereof*** appellants have conceded what is to be considered as prior art in determining obviousness of their improvement.") (emphasis added); *see also PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007) ("Admissions in the specification regarding the prior art are binding on the patentee for purposes of a later inquiry into obviousness.").

B. A POSA would have selected admitted prior art Compound 338 as a lead compound for modification based on the Pfizer SAR Papers.

Based on the prior art, a POSA would have known that a lead molecule for a selective CDK4 inhibitor should have an IC50 potency against CDK4 in the single-digit to low double-digit nanomolar range. FOF at ¶ 29. Table 4 of the '355 and '630 patents discloses that Compound 338 has an IC50 potency against CDK4 in this range. *Id.* at ¶ 30. Dr. Micalizio and Dr. Toogood agreed that a POSA also would have used the data for Compound 338 in Brain PCT as a guide to select a lead compound. *Id.* at ¶ 31. Consistent with the Table 4 data, a POSA would have understood that Compound 338 was among the most potent compounds for CDK4 disclosed in Brain PCT, although it was not among the most selective. *Id.* at ¶ 32.

From the Pfizer SAR Papers, a POSA would have known that palbociclib (identified in Toogood 2005 as compound 43) is a "remarkably potent and selective" CDK4 inhibitor. FOF at ¶ 11. Plaintiffs' expert, Dr. Toogood, testified that a POSA would have looked to information on palbociclib in their pursuit of a new selective CDK4 inhibitor, and would have been motivated to achieve at least the selectivity disclosed in the Pfizer SAR Papers. *Id.* at ¶ 33.

Unrebutted testimony showed that the Pfizer SAR Papers teach a POSA that a potent CDK4 inhibitor should contain the following structural motifs to interact with the CDK4 enzyme in four key regions:

> (1) an amino pyrimidine group to dock the compound into the hinge region of the ATP binding site and orient the compound to

> interact with the other three regions. *Id.* at ¶ 34.
>
> (2) an aromatic group at the C2 position para substituted with a piperazine group to occupy the specificity surface. *Id.*
>
> (3) a cyclopentyl group to occupy the ribose/phosphate site. *Id.*
>
> (4) an out-of-plane carbonyl-containing group to interact with the Phe80 pocket. *Id.*

A POSA would have recognized that Compound 338 contains all of these structural motifs and that the teachings of the Pfizer SAR Papers could successfully be applied to Compound 338. FOF at ¶ 35; *see also* Tr. at 471:16-19 (Dr. Toogood conceding that decisions about which compounds to make and test are often guided by what has been learned in earlier SAR iterations).

A POSA also would have known from the Pfizer SAR Papers that selectivity for CDK4 would be improved on a potent (but relatively non-selective) CDK4 inhibitor by replacing the carbon-containing phenyl group at the C2 position with a nitrogen-containing pyridyl group—the so-called "magic N". FOF at ¶ 36.

Thus, a POSA reading the Pfizer SAR Papers would have recognized Compound 338 as a lead for further modification, due to its structural similarity with palbociclib and its disclosure in Table 4 and/or Brain PCT as a potent, but relatively non-selective, CDK4 inhibitor. *Id.* at ¶ 37; *see also Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008-09 (Fed. Cir. 2009) (finding that the district court was not clearly erroneous by employing a flexible approach and concluding that the defendants had raised a substantial question that one of skill in the art would have considered potency of the prior art compound as a starting point from which to pursue further development efforts).

C. A POSA would have been motivated to modify Compound 338 by inserting the "magic N" to achieve ribociclib, with more than a reasonable expectation of success.

A POSA also would have been motivated to install the "magic N" on Compound 338 to

achieve ribociclib, with more than a reasonable expectation of success. Obviousness based on structural similarity may be proven by the identification of some motivation that would have led one of ordinary skill in the art to select and modify a known compound in a particular way to achieve the claimed compound. *Altana*, 566 F.3d at 1007. Here, as discussed above, Compound 338 possesses all the molecular features of palbociclib that made it attractive as a potent and selective CDK4 inhibitor, *except* the "magic N." FOF at ¶ 38. But Toogood 2005 had identified palbociclib as displaying "a superior overall profile, including the combined attributes of potency, selectivity, and pharmaceutical properties," (*Id.* at ¶ 39) and made it clear that the "magic N" pyridyl group was the key factor in this compound's selectivity for CDK4. *Id*. Further, Toogood 2005 noted that the effect of the "magic N" in conferring a high level of selectivity "appears to be general and to apply across a wide range of kinases." *Id*. Thus, a POSA would have been highly motivated to modify Compound 338 by installing the "magic N" on the C2 phenyl group, and a POSA would have reasonably expected to achieve a CDK4 inhibitor with superior properties, including a high level of selectivity for CDK4. *Id.* at ¶ 40.

Further buttressing the reasonable expectation of success, a POSA would have been reasonably capable of overlaying the Compound 338 core structure with the palbociclib core structure to determine that the C2 side chain in both palbociclib and Compound 338 (as modified with the "magic N") would lie within the same region of space—the "specificity surface" of CDK4. *Id.* at ¶ 41. Since these C2 side chains lie within the same space, a POSA would have reasonably expected the "magic N" modification on Compound 338 to confer the same general benefit it conferred on the compounds discussed in the Pfizer SAR Papers. *Id.* at ¶ 42.

While the prior art taught that the "magic N" modification slightly decreased potency for CDK4, this would not have dissuaded a POSA from making the modification. *Id.* at ¶ 43. In several

instances, the potency drop was, at most, from single-digit nanomolar to low-double-digit nanomolar, which was still within the desired potency range for a CDK4 inhibitor. *Id.* Further, VanderWel discloses that there was "a subtle balance between the two desirable properties of selectivity and potency," which "suggested that the optimal inhibitor may not be the most potent." *Id.* at ¶ 44; *see also* Tr. 470:10-15 (Dr. Toogood conceding that a POSA would know that potency of CDK4 inhibitors had to be balanced against their selectivity for CDK4). A POSA would have understood from VanderWel that a small sacrifice of potency in favor of a large gain in selectivity was a desirable modification. *Id.* at ¶ 44; *see also* Tr. 502:20-503:8 (Dr. Toogood conceding that a five-and-a-half-fold drop in potency with palbociclib still achieved remarkable potency and selectivity). Thus, a POSA still would have had ample motivation in the art to make the modification of Compound 338 with a reasonable expectation of success. FOF at ¶ 45.

Accordingly, a POSA would have been motivated to modify Compound 338 to arrive at ribociclib, with more than a reasonable expectation of success. For this reason, claim 1 of the '355 patent would have been obvious over Compound 338 in view of the Pfizer SAR Papers.

D. Claim 6 of the '630 patent is obvious over Compound 338 in view of the Pfizer SAR Papers and Fry.

Claim 6 of the '630 patent recites a method for the treatment of cancer by inhibiting a cyclin-dependent kinase (CDK) comprising administration of an effective amount of ribociclib or a pharmaceutically acceptable salt thereof to a subject in need of treatment thereof, wherein the cancer is carcinoma of the breast. FOF at ¶ 46. Fry would have taught a POSA that selective inhibitors of CDK4 could be used as a treatment for breast cancer. *Id.* at ¶ 47. In particular, Fry disclosed that palbociclib exhibited "robust antitumor activity" in a breast carcinoma cell line *in vivo*. *Id.* at ¶ 47. Since the motivation to modify Compound 338 is based on a similar modification to palbociclib, a POSA would have reasonably expected that the resultant compound, ribociclib,

could be used in similar methods to treat similar cancers. *Id.* at ¶ 48. Accordingly, a POSA would have had motivation and a reasonable expectation of success to modify Compound 338 to achieve a compound, ribociclib, useful in a method of treating breast carcinoma.

E. Secondary Considerations do not outweigh the *prima facie* obviousness.

At trial, Plaintiffs contended that unexpected results, long-felt but unmet need, acquiescence of others, failure of others, skepticism of others, industry praise, and commercial success of ribociclib support non-obviousness. However, "[w]hile secondary considerations must be taken into account, they do not necessarily control the obviousness determination." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014).

For unexpected results, Plaintiffs rely on ribociclib's G^1-cell cycle block and clinical data that ribociclib plus a second agent exhibits improved overall survival in breast cancer patients versus that second agent alone. But neither should move the needle on the obviousness inquiry. "[E]vidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art ***at the time of the invention***." *Id*. (emphasis added). Rather, the record shows that a POSA would have expected installation of the "magic N" on Compound 338 to make it more selective, and thus to cause a G^1 block. FOF at ¶ 49. And further, since the prior art disclosed that palbociclib exhibited antitumor activity (*Id.*), a POSA would have expected ribociclib to have at least some clinical benefit in cancer patients. *Id*. The record also shows that a POSA would have an expectation that a drug would be efficacious for a trial's endpoints. *Id.* at ¶ 50.

Plaintiffs' expert, Dr. Cohen, failed to correctly apply the legal standard to his analysis of a long-felt but unmet need, and introduced entirely new theories at trial. The patentee bears the burden of production for long-felt, but unmet need, as with all secondary considerations, and must

show an articulated identified problem and evidence of efforts to solve the problem before the invention. *Apple Inc. v. Samsung Elec. Co., Ltd.*, 816 F.3d 788, 804 (Fed. Cir. 2016) *vacated* 839 F.3d 1034 (Fed. Cir. 2016) (*en* banc). Determining whether the need is "long-felt" is assessed from the time elapsing between when the need was identified and the filing date of the patent. *Ecolochem Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000). Moreover, to meet the burden of production, a need must actually be shown, not simply presumed. *In re Courvaras*, 70 F.4th 1374, 1382 (Fed. Cir. 2023).

Plaintiffs' expert, Dr. Cohen, did not rely on any reference that pre-dates the '630 and '355 patents' priority date in forming his opinions regarding long-felt need. FOF at ¶ 51. Dr. Cohen also did not rely on his own experiences to establish a long-felt need; however, any attempt would be futile because Dr. Cohen was not an oncologist until two years ***after*** the priority date. *Id.* at ¶ 52. Additionally, Dr. Cohen's long-felt need opinions were entirely new and improperly presented for the first time at trial. *Id.* at ¶ 53. Even if Dr. Cohen had properly shown a need, he also agreed that there remains a need to improve metastatic breast cancer treatments. *Id.* at ¶ 54.

Plaintiffs' expert, Dr. Toogood, asserts that acquiescence of the industry and failure of others to make CDK inhibitors supports nonobviousness. However, Dr. Toogood makes clear that he has no knowledge or references to show why others opted not to litigate the patents-in-suit and ***why*** others chose not to continue their CDK inhibitor programs. *Id.* at ¶ 55.

Plaintiffs' expert, Dr. Cohen, also alleged that the asserted claims support skepticism of others and industry praise. An expert's opinion that improperly applies legal principles is unlikely to be relevant to the Court's fact-finding. *Sprint Commc'ns Co. L.P. v. Cox Commc'ns Inc.*, 302 F.Supp.3d 597, 624 (D. Del. 2017); FED. R. EVID. 702(d). Indeed, Dr. Cohen admitted that he did not apply any legal standard to his analyses, and thus his testimony is unhelpful to the Court. *Id.*

at ¶ 56.

Finally, Plaintiffs, through their expert Dr. Vellturo, alleged that Kisqali is a commercial success that supports nonobviousness of the asserted claims. However, Dr. Vellturo failed to consider relevant marketing and other expense data, as well as unasserted patents listed in the Orange Book for Kisqali. *Id.* at ¶ 57. Thus, Dr. Vellturo's opinions fail to establish whether Kisqali is in fact a commercial success, as well as whether commercial success can be specifically attributed to the patents-in-suit.

Plaintiffs have failed to introduce any evidence of secondary considerations sufficient to overcome the evidence of obviousness. Defendants reserve the right to respond to Plaintiffs' specific assertions of secondary considerations in their Responsive Brief.

III. MSN HAS PROVEN THAT CLAIM 1 OF THE '355 PATENT AND CLAIM 6 OF THE '630 PATENT ARE INVALID FOR OBVIOUSNESS-TYPE DOUBLE PATENTING OVER CLAIM 7 OF THE '225 PATENT IN VIEW OF THE PFIZER SAR PAPERS

The asserted claims of the '355 and '630 patents are invalid for obviousness-type double patenting over claim 7 of the '225 patent in view of the Pfizer SAR Papers. In view of the Pfizer SAR Papers, a POSA would have selected Compound 338 from the thirty-three compounds listed in claim 7 and made obvious modifications to arrive at claim 1 of the '355 patent and claim 6 of the '630 patent.

A. Claim 7 encompasses using the recited compounds for inhibiting CDK4 and treating breast cancer.

Obviousness-type double patenting prohibits "claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent." *Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1384 (Fed. Cir. 2010). The proper analysis of obviousness-type double patenting requires a two-step analysis: First, the court construes the claims in the earlier patent and the claims in the later patent and determines the differences; second, the court

determines whether those differences render the claims patentably distinct. *Id.* A later claim that is not patentably distinct from, i.e., is obvious over or anticipated by, an earlier claim is invalid for obviousness-type double patenting. *Id.*

Claim 7 of the '225 patent recites thirty-three compounds. However, "[s]tanding alone, that claim does not adequately disclose the patentable bounds of the invention." *Geneva Pharms. Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1385 (Fed. Cir. 2003). Rather, "to ascertain the scope of the earlier patent's claim to the compound itself, we had to examine the specification of the earlier patent, including the compound's disclosed utility." *Sun Pharm.*, 611 F.3d at 1385. And this analysis "extends to any and all such uses disclosed in the specification of the earlier patent." *See Id.* at 1387. Here, the '225 patent discloses uses of the disclosed compounds for inhibiting CDK4 and treating breast cancer. FOF at ¶ 59. Accordingly, claim 7 encompasses use of the thirty-three recited compounds for inhibiting CDK4 and treating breast cancer.

B. A POSA would have selected Compound 338 from the thirty-three compounds listed in claim 7.

Given that claim 7 covers not only the thirty-three compounds it recites but encompasses their use in methods of treating breast cancer and inhibiting CDK4, it would have been obvious to apply the teachings of the Pfizer SAR Papers to modify them. Even independent of their uses, however, a POSA looking at the structures of the compounds claimed in claim 7 would have perceived them as CDK inhibitors due to their structural similarity with palbociclib. *Id.* at ¶ 60. Also, based on the Pfizer SAR Papers, a POSA would have narrowed the group of thirty-three compounds based on their similar structural motifs as palbociclib—and, ultimately, a POSA would have selected Compound 338 from the compounds listed in claim 7 for further modification. *Id.* at ¶ 61.

C. A POSA would have been motivated to modify Compound 338 by inserting the "magic N" to achieve ribociclib, with more than a reasonable expectation of success.

As discussed above in Section II.C, a POSA would have had ample motivation from the Pfizer SAR Papers, and Toogood 2005 in particular, to modify Compound 338 via insertion of the "magic N." Further, a POSA reasonably would have expected this modification to work from the disclosures of the Pfizer SAR Papers themselves, for the reasons identified in that section. The doctrine of obviousness-type double patenting operates to prevent a common assignee from "obtaining more than one valid patent for either (a) the 'same invention', or (b) an 'obvious' modification of the same invention." *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985). This is true for chemical species claimed in a later-filed patent that are obvious modifications of chemical species claimed in an earlier-filed patent. *See id.* at 895–896. Accordingly, claim 1 of the '355 patent is patentably indistinct from claim 7 of the '225 patent, and thus invalid for obviousness-type double patenting.

D. Claim 6 of the '630 patent is likewise invalid for obviousness-type double patenting.

As discussed above in section III.A, claim 7 of the '225 patent not only claims the thirty-three compounds it recites, but the claim encompasses their use in treating breast cancer and inhibiting CDK4 activity.[2] Because Compound 338 and ribociclib show a "'sufficiently close relationship . . . to create an expectation' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old," *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) (*quoting In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990), it follows that a POSA would have expected that modified Compound 338 (i.e., ribociclib)

[2] The construction of claim 7 of the '225 patent was not in dispute. *See* Pretrial Order Exhibit A at page 17.

could be used in the uses encompassed by claim 7 of the '225 patent.

Even without drawing such a conclusion, however, claim 6 is obvious. As discussed above in section II.D, a POSA would have had ample motivation from the Pfizer SAR Papers and Fry to use the modified Compound 338 (i.e., ribociclib) in a method of treating cancer, particularly breast cancer, with a reasonable expectation of success.

Accordingly, claim 6 of the '630 patent is patentably indistinct from claim 7 of the '225 patent, and thus is invalid for obviousness-type double patenting.

IV. MSN HAS PROVEN THAT CLAIM 1 OF THE '225 PATENT IS INVALID AS NOT DESCRIBED AND NOT ENABLED

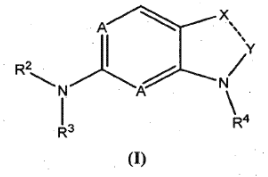
A. The '225 patent's claims are not described by the specification in a way to show that the inventors had possession of the claimed invention.

Claim 1 of the '225 patent defines a genus of compounds. "Written description of an invention claimed as a genus of chemical compounds, as here, raises particular issues because . . . written description of a broad genus requires description not only of the outer limits of the genus but also of either a representative number of members of the genus or structural features common to the members of the genus, in either case with enough precision that a relevant artisan can visualize or recognize the members of the genus." *Regents of the Univ. of Minnesota v. Gilead Scis., Inc.*, 61 F.4th 1350, 1356 (Fed. Cir. 2023). This requires "an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

1. The recitation of a single functional group in a laundry list of substituents is legally insufficient to provide *ipsis verbis* written description for a subgenus containing that substituent.

The '225 patent's written description problem stems from the applicants narrowing their

claims to a particular subgenus approximately four years after filing. The initial claims and specification describe a compound having the following formula:



(I)

JTX0006A-1633. The definitions of the groups were much broader than in the claim: for instance, the dashed line between X and Y could be a single or double bond. *Id.* When that dashed line was a double bond, X could be N or CR^{11} and Y could be CR^{12}. *Id.* R^{11} and R^{12} could be each, independently, selected from one of twenty-three listed moieties. FOF at ¶ 63. But during prosecution, the applicants amended the claim such that the dashed line could only be a double bond, X had to be CR^{11}, Y had to be CR^{12}, R^{11} was limited to "hydrogen or C_1-C_3 alkyl," and R^{12} was restricted to only being $BC(O)NR^{13}R^{14}$; these limitations remain in the present claim. *Id.* at ¶ 64.

The specification can only provide written description support for this subgenus if the original application provides adequate direction which reasonably would lead a POSA to the subgenus. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570 (Fed. Cir. 1996). Such direction, for a chemical genus, may come from either *ipsis verbis* written description support or "blaze marks" in the specification leading a POSA to the claimed subgenus. *See id.* The specification, as filed, provides neither, and thus the claims are invalid as inadequately described. *See Ariad Pharms.*, 598 F.3d at 1348 ("prohibiting adding new matter to the claims has properly been held enforceable under § 112, first paragraph.") (citing *In re Rasmussen*, 650 F.2d 1212, 1214-15 (C.C.P.A. 1981)).

There is simply no written description for the issued claim in the original application. The Federal Circuit has held that "just because a moiety is listed as one possible choice for one position does not mean there is *ipsis verbis* support for every species or sub-genus that chooses that moiety.

Were this the case, a 'laundry list' disclosure of every possible moiety for every possible position would constitute a written description of every species in the genus. This cannot be because such a disclosure would not 'reasonably lead' those skilled in the art to any particular species." *Fujikawa*, 93 F.3d at 1571. Thus, the specification's recitation, at filing, of twenty-three possible moieties that could be "independently selected" for R^{11} and R^{12} simply does not provide written description for the subgenus where R^{11} is selected from H and C_1-C_3 alkyl and R^{12} as "$BC(O)NR^{13}R^{14}$." *Compare* FOF at ¶ 65 *with* FOF at ¶ 64. There is thus no *ipsis verbis* support for the claimed subgenus.

Furthermore, there are no "blaze marks" to the claim language, either. Dr. Toogood pieces together elements of four different dependent claims and picks and chooses from the laundry list of moieties to find "blaze marks" pointing to support for claim 1. *Id.* at ¶ 66. In particular, he limits the dashed line in the original claim to being a double bond, combines the limitations of original claim 1, original claim 5, and original claim 11, and then selects R^{11} as "H or C_1–C_3 alkyl" from a laundry list of twenty-three different possible moieties, and R^{12} as $BCONR^{13}R^{14}$ from the same list *Id.* at ¶ 67. But this *post-hoc* exercise of looking for the issued claims in the specification as filed is nothing more than a "maze-like path, each step providing multiple alternative paths, [which] is not a written description of what might have been described if each of the optional steps had been set forth as the only option." *Regents of the Univ. of Minnesota*, 61 F.4th at 1357. Thus, the recitation of these groups within the specification as possible options cannot constitute written description for the subgenus that was eventually claimed.

For the first time on cross-examination, Dr. Toogood attempted to recast the thirty-three disparate compounds within the specification that fall within the claim language as "blaze marks" to the claimed genus. FOF at ¶ 68. But that is both legally and factually insufficient. Rather, for

structures in a specification to serve as a "blaze mark," the common structural features within the disclosure "must constitute the near-entirety of the structures being compared" with the claimed structure. *See Univ. of Minnesota*, 61 F.4th at 1358. Dr. Toogood never offered any reason why a POSA, in particular, would draw a line around *those* thirty-three compounds within the specification, versus the remaining 400+ compounds, to arrive at the claimed subgenus. Rather, as Dr. Micalizio testified, there is no "blaze mark" towards these compounds or the claimed subgenus because compounds that fall both inside and outside of the subgenus are disclosed as being potent at their biological target. FOF at ¶ 69.

The thirty-three compounds thus cannot serve as "blaze marks." Instead, "the structures here are so extensive and varied" that they "encompass a significantly larger genus than that claimed" and are "not sufficiently common to that of [claim 1 of the '225 patent] to provide written description support. *See Univ. of Minnesota*, 61 F.4th at 1358. As Dr. Micalizio testified, the examples in the '225 patent specification provide a very small glimpse of the much larger number of species that would fall within the claimed genus, and do not show compounds having all of the structural features recited in the claim. FOF at ¶ 70. Thus, there is neither support for the claim language in the words of the specification, nor are there "blaze marks" to the subgenus, either.

2. The specification provides insufficient representative species to describe claim 1 to a POSA.

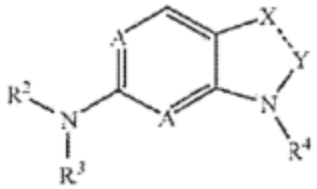
Finally, there are not sufficient representative examples to provide written description support for the claimed subgenus. "[M]erely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species." *Ariad Pharms.*, 598 F.3d at 1350. Rather, as Dr. Micalizio testified, there are insufficient representative species to provide support for the full scope of the R^3 and R^{12} groups recited in claim 1. FOF at ¶ 72. Furthermore, Dr.

Toogood offers no opinion that the thirty-three compounds recited in the specification are sufficiently representative to describe the claimed genus or that the inventors were in possession of the claimed invention. *Id.* Particularly considering the infinite scope of claim 1 due to the construction of "substituted" (*Id.* at ¶ 71) the thirty-three examples listed in the specification cannot be sufficient to provide written description support. Claim 1 is thus invalid as lacking written description.

B. Claim 1 is not enabled by the specification.

Claim 1 of the '225 patent is not enabled because the specification does not do enough to teach a POSA how to both make and use the vast number of compounds claimed. The Supreme Court, on this point, has spoken plainly: "if a patent claims an entire class of . . . compositions of matter, the patent's specification must enable a person skilled in the art to make ***and use*** the ***entire*** class." *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023) (emphasis added). This standard is met when there is "sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species ***among all those encompassed by the claimed genus*** possess the disclosed utility." *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991) (emphasis added). Thus, to enable claim 1, the specification of the '225 patent must guide a POSA not only how to make the compounds claimed, but also to identify those compounds in the genus that are useful.

The '225 patent specification does not do so. First, the full scope of the claims covers a practically infinite number of compounds. As noted above, the general structure of the compounds of claim 1 is:



wherein the dashed line is a double bond, X is CR^{11}, Y is CR^{12}, and CR^{12} is —$BC(O)NR^{13}R^{14}$. JTX0001-0126. R^3, R^{13} and R^{14} may be one of several moieties that are "substituted." JTX0001-0127. Because the R^3, R^{13}, and R^{14} groups may include "substituted" moieties, and because the substituents on those moieties may themselves "be further substituted" under the agreed-upon claim construction, the claims encompass an infinite number of compounds. FOF at ¶ 73. In addition, the specification provides a very long list of potential substituents, which is recited over the course of nearly a full column of text, and which uses non-limiting, open-ended language to indicate other unrecited substituents may be included, too. *Id.* at ¶ 74. Thus, the scope of the claims is exceptionally broad.

Second, the specification does not offer much—if any—guidance on how to pick and choose moieties at these positions that will result in ***useful*** compounds. The '225 patent specification discloses that the compounds are useful in treating proliferative disease and modulating activity of over seventy different kinases, including kinase families such as CDK and JAK. *Id.* at ¶ 75. But the specification does not provide any text or description as to how to choose substituents that render the claimed molecules active at any particular kinase outside of the working examples, and for those it only discloses biological data for compounds at CDK1, CDK2, CDK4 and JAK3. *Id.* at ¶ 76. To the extent a compound was not found to have biological activity at one of these kinases, however, a POSA would still need to test it to determine whether it had activity at any of the other 70+ kinases disclosed in the specification and was thus a "useful" compound. *Id.* at 77.

Third, the specification's working examples do not guide a POSA to the full scope of useful compounds. The specification discloses over 450 different molecules, but only thirty-three that fall within the scope of the claims because of the substituent at C6. *Id.* at 78. And the structural diversity within those working examples is so narrow that it cannot enable the full scope of the claims. For instance, while the patent claims recite that the R^3 can be "substituted C_3-C_8 cycloalkyl [or] substituted heterocyclyl," there are no examples of claimed compounds with R^3 bearing these groups. *Id.* at ¶ 79. There are only two examples of claimed compounds where R^3 is a one-carbon linker (C_1 alkyl) substituted with an aryl group. *Id.* For the claimed compounds, when R^3 is substituted phenyl or substituted heteroaryl, it is almost always substituted with piperazine at the *para* position. *Id*. And even looking outside the claims, there are only a small handful of examples—approximately sixteen—where the R^3 group is something *other* than a substituted aryl or heteroaryl group, and very few of those have any biological activity telling a POSA whether they are useful or not. *Id.* at ¶ 80. Looking at the R^{12} position, there is limited variability: there are no examples where "B" is anything other than a bond; the only examples in which R^{13} and R^{14} are both something other than hydrogen, both are methyl groups (rather than demonstrating independent selection of the substituents at this position); and there are no examples where R^{13} or R^{14} are C_3-C_8 cycloalkyl, substituted C_1-C_3 alkyl, substituted C_3-C_8 cycloalkyl, or substituted heterocyclyl. *Id.* at ¶ 81. Thus, given the limited structural diversity of the examples in comparison to the claim, along with the lack of biological data, a POSA would need to engage in trial-and-error experimentation to find useful compounds within the claim scope.

Thus, undue experimentation would be required to practice the claims. In other, similar cases, the Federal Circuit has found claims directed to a broad class of compounds not enabled where extensive trial-and-error experimentation would be needed to identify useful compounds.

For instance, in *Wyeth & Cordis Corp. v. Abbott Lab'ys*, 720 F.3d 1380, 1385 (Fed. Cir. 2013), the Federal Circuit held that claims encompassing "at least tens of thousands of candidate[]" compounds, that "[t]he specification is silent about how to structurally modify . . . , let alone in a way that would preserve the recited utility," were not enabled because "it would be necessary to first synthesize and then screen *each* candidate compound using the assays disclosed in the specification" to determine whether it was useful. The Federal Circuit then held that "having to synthesize and screen each of at least tens of thousands of candidate compounds constitutes undue experimentation." *Id.* Here, even Dr. Toogood recognizes that the compounds recited in claim 1 are intended for therapeutic use but offers no opinion on the quantity of experimentation a POSA would need to do in order to identify useful compounds from useless ones. *Id.* at ¶ 82. Dr. Micalizio testified that if the compounds are not constrained by their function as kinase inhibitors, then the claim extends to an infinite collection of compounds that would require undue experimentation to make and use. Tr. 132:22–133:4 (Micalizio). Further, if the claims are constrained by function, there is not enough guidance in the specification to tell a POSA how to make compounds that achieve that function. Tr. 133:5–25 (Micalizio). Accordingly, claim 1 is not enabled.

V. CONCLUSION

For the foregoing reasons, the Court should issue judgment in favor of MSN that claim 1 of the '355 patent, claim 6 of the '630 patent, and claim 1 of the '225 patent are invalid.

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CERTIFICATE OF SERVICE

I, Karen L. Pascale, Esquire, hereby certify that on March 1, 2024, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF (which will send notification that such filing is available for viewing and downloading to all registered counsel), and in addition caused true and correct copies of the foregoing document to be served upon the following counsel of record by electronic mail:

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